

FORM PTO-1590 (Modified)
(REV 10-95)

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NUMBER

TRANSMITTAL LETTER TO THE UNITED STATES
DESIGNATED/ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 U.S.C. 371

MERCK 2047

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR

09/446298

INTERNATIONAL APPLICATION NO.

PCT/EP98/03525

INTERNATIONAL FILING DATE

10 June 1998

PRIORITY DATE CLAIMED

20 June 1997

TITLE OF INVENTION

HOLDING DEVICE FOR MONOLITHIC SORBENTS

APPLICANT(S) FOR DO/EO/US

Dieter LUBDA, et al.



Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
 - a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☒ has been transmitted by the International Bureau.
 - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ A copy of the International Search Report (PCT/ISA/210).
8. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
 - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☐ have been transmitted by the International Bureau.
 - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
 - d. ☒ have not been made and will not be made.
9. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
10. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 13 to 18 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☐ A **FIRST** preliminary amendment.
A **SECOND** or **SUBSEQUENT** preliminary amendment.
16. ☐ A substitute specification.
17. ☐ A change of power of attorney and/or address letter.
18. ☐ Certificate of Mailing by Express Mail
19. ☒ Other items or information:

Letter

U.S. APPLICATION NO. (IF KNOWN) SEE CFR

INTERNATIONAL APPLICATION NO.

ATTORNEY'S DOCKET NUMBER

09/7446298

PCT/EP98/03525

MERCK 2047

20. The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :

- ☒ Search Report has been prepared by the EPO or JPO **\$840.00**
- ☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) **\$670.00**
- ☐ No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) **\$760.00**
- ☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO **\$970.00**
- ☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) **\$96.00**

ENTER APPROPRIATE BASIC FEE AMOUNT =**\$840.00**Surcharge of **\$130.00** for furnishing the oath or declaration later than months from the earliest claimed priority date (37 CFR 1.492 (e)). ☐ 20 ☐ 30**\$0.00**

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	3 - 20 =	0	x \$18.00	\$0.00
Independent claims	1 - 3 =	0	x \$78.00	\$0.00
Multiple Dependent Claims (check if applicable)			<input type="checkbox"/>	\$0.00

TOTAL OF ABOVE CALCULATIONS =**\$840.00**Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28) (check if applicable). ☐**\$0.00****SUBTOTAL =****\$840.00**Processing fee of **\$130.00** for furnishing the English translation later than months from the earliest claimed priority date (37 CFR 1.492 (f)). ☐ 20 ☐ 30 +**\$0.00****TOTAL NATIONAL FEE =****\$840.00**Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) (check if applicable). ☐**\$0.00****TOTAL FEES ENCLOSED =****\$840.00**Amount to be:
refunded
charged

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- ☒ A check in the amount of **\$840.00** to cover the above fees is enclosed.
- ☐ Please charge my Deposit Account No. _____ in the amount of _____ to cover the above fees.
A duplicate copy of this sheet is enclosed.
- ☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. **13-3402** A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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Filed: 12/20/99
AJZ:jvbp

SIGNATURE

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27,969

REGISTRATION NUMBER

20 December 1999

DATE

Holding device for monolithic sorbents

The invention relates to holding devices for monolithic sorbents for chromatography.

- 5 During packing of chromatography columns with particulate sorbents, the sorbent bed comes into close contact with the jacket of the column. If, as disclosed in WO 94/19 687 and in WO 95/03 256, particulate
- 10 sorbents are replaced by monolithic sorbents, the problem arises of sealing the jacket of the sorbent so as to be liquid-impermeable, pressure-resistant and inert to the eluents. Only in this way is it ensured that the eluent flows exclusively through the sorbent.
- 15 F. Svec and J. M. Frechet (1992) Anal. Chem. 64, pages 820 - 822, describe how a monolithic sorbent can be polymerized into a tube. This principle is of only limited applicability in the case of ceramic sorbents, since the green compact shrinks during the subsequent
- 20 firing and calcination steps: this process can only be used if the internal diameter of the tube is sufficiently small, i.e. significantly less than one centimetre. A holding device which can also be used for thicker monolithic sorbents is disclosed in
- 25 WO 94/19 687: a Teflon casing surrounds the ceramic rod. So that this casing provides liquid-impermeable sealing even if the operating pressure of the chromatography device is applied in the interior, the Teflon-encased ceramic rod is located in a metal pipe
- 30 of relatively large internal diameter in which a counterpressure is generated.

- The device disclosed in WO 94/19 687 has a complex construction. The object is thus to provide simplified
- 35 holding devices and casings for monolithic sorbents.

The invention relates to encased monolithic sorbents based on porous mouldings, in particular those which have interconnected macropores and mesopores in the

walls of the macropores, where the diameter of the macropores has a median value of greater than 0.1 μm and where the diameter of the mesopores has a median value of 2 and 100 nm, the outer surface of said
5 monolithic sorbent being surrounded in a liquid-impermeable manner by a pressure-resistant plastic casing.

The invention also relates to the use of a monolithic sorbent according to the invention in a chromatographic column or a chromatographic cartridge.
10

The invention furthermore relates to the use of a monolithic sorbent according to the invention in the chromatographic separation of at least two substances.
15

Figure 1 shows a monolithic sorbent encased in accordance with the invention in a holding device; the upper half is shown. Figures 2 and 3 show variants for holding monolithic sorbents.
20

Monolithic sorbents are known in principle from the literature; they include, in particular, porous ceramic mouldings, as disclosed in WO 94/19 687 and WO 95/03 256. The term monolithic sorbents in the broader sense also includes mouldings made from polymers, as described by F. Svec and J. M. Frechet (1992) Anal. Chem. 64, pages 820 - 822, and by S. Hjerten et al. (1989) J. Chromatogr. 473, pages 273 -
25 275. Particular preference is given to monolithic sorbents based on porous mouldings which have interconnected macropores and mesopores in the walls of the macropores, where the diameter of the macropores has a median value of greater than 0.1 μm and where the diameter of the mesopores has a median value of 2 and
30 100 nm.
35

Monolithic sorbents thus consist of materials as used for particulate sorbents. In many cases (for example

SiO₂), these sorbents can be used directly for chromatographic separation. More frequently, however, the basic supports are derivatized in order to improve the separation properties; additional groups grouped together under the term separation effectors are introduced.

Separation effectors and processes for their introduction into the basic supports are known in principle to the person skilled in the art. Examples of reactions by means of which separation effectors can be introduced are the following:

- a) Derivatization using silane derivatives of the formula I



in which

- X is methoxy, ethoxy, halogen or amino derivatives,
R¹ is C₁-C₅-alkyl,
n is 1, 2 or 3

and

- R² has one of the following meanings:

- a1) unsubstituted or substituted alkyl or aryl, such as, for example, n-octadecyl, n-octyl, benzyl or cyanopropyl;
a2) anionic or acidic radicals, such as, for example, carboxypropyl;
a3) cationic or basic radicals, such as, for example, aminopropyl, diethylaminopropyl or triethylammoniumpropyl;
a4) hydrophilic radicals, such as, for example, (2,3-dihydroxypropyl)oxypropyl;
a5) activated radicals capable of bonding, such as, for example, (2,3-epoxypropyl)oxypropyl.

- b) Adsorption or chemical bonding of polymers, such as polybutadiene, siloxanes, polymers based on styrene-divinylbenzene, on (meth)acrylic acid derivatives or on other vinyl compounds, and on peptides, proteins, polysaccharides and polysaccharide derivatives to the basic support;
- c) Chemical bonding of polymers mentioned under b) via the derivatives mentioned under a); these include graft polymers of poly(meth)acrylic acid derivatives on diol-modified silica gel in accordance with EP-B-0 337 144.
- d) Adsorption or chemical bonding of chiral phases, such as, for example, amino acid derivatives, peptides or proteins, or of cyclodextrins, polysaccharides or polysaccharide derivatives.

Further customary derivatization possibilities and derivatization processes are known to the person skilled in the art and are described in the common handbooks, such as Unger, K. K. (ed.), Porous Silica, Elsevier Scientific Publishing Company (1979) or Unger, K. K., Packings and Stationery Phases in Chromatographic Techniques, Marcel Dekker (1990).

Further examples of various separation effectors and of processes for introducing separation effectors into monolithic sorbents are given in the following publications:

- a) DE 38 11 042 discloses, inter alia, monomers which are suitable for the preparation of ion exchangers; these include, for example, acrylic acid, N-(sulfoethyl)acrylamide, 2-acrylamido-2-methylpropanesulfonic acid, N,N-dimethylaminoethylacrylamide, N,N-diethylaminoethylacrylamide and trimethylammoniummethylacrylamide.

Other monomers mentioned in this document allow the bonding of affinity ligands or of enzymes, or are suitable for reversed phase chromatography: these include, for example, acrylic acid, acrylamide, allylamine and acrylonitrile.

b) DE 43 10 964 discloses monomers containing an oxirane ring, an azlactone ring or a group which can be converted into an azlactone ring. Polymers containing monomers of this type are particularly suitable for binding affinity ligands or enzymes. Affinity ligands are disclosed by way of example in DE 43 10 964.

The epoxide groups in such polymers can furthermore advantageously be reacted further, allowing the preparation of ion exchangers, thiophilic sorbents or sorbents for metal chelate or hydrophobic chromatography. Here, phosphoric acid, diethylamine, trimethylamine, sulfurous acid or complexing agents, such as iminodiacetic acid, can be added onto the oxirane ring.

The preparation of thiophilic sorbents and sorbents for metal chelate chromatography is disclosed in DE 43 10 964.

DE 43 33 674 and DE 43 33 821 disclose reactions by means of which ion exchangers can be prepared.

DE 43 23 913 describes sorbents for hydrophobic interaction chromatography.

The term "monolithic sorbent" is taken to mean, in accordance with the invention, both a porous base element and a porous base element derivatized by means of separation effectors.

The object is achieved in a simplified manner by encasing the monolithic sorbent as described in WO 94/19 687 with Teflon, PTFE or FEP, for example by shrinking-on a thin-walled tube. In a second step, a further pressure-resistant covering is then provided. To this end, the monolithic sorbent encased in the thin-walled tube is cast in a tube containing synthetic resin, for example an epoxy or polyimine resin, or sintered with a plastic. Additional covering with a laminate material with glass or carbon fibre reinforcement is also suitable for pressing the inner casing tightly against the monolithic sorbent.

The simplest solution is to apply a sufficiently pressure-resistant and solvent-resistant plastic casing to the monolithic sorbent. Plastics which are suitable for this application are known, for example polyether ketones, such as polyether ether ketones (PEEK). These plastics can be applied to the monolithic sorbent in the form of a powder and subsequently melted or sintered. PTFE is also suitable for application by sintering.

Another way of producing monolithic sorbents encased in this way is to extrude the plastic onto the ceramic rod. In this case, the ceramic rod is fed through a crosshead die in parallel to the extrusion of a tube. The freshly extruded tube surrounds (hot) the ceramic rod and is additionally pressed against the ceramic rod, for example by a pressure device. It is also possible to warm a pre-shaped tube instead of producing a tube by extrusion. This mechanical pressing and additional sintering during cooling produce a tight casing. It is also possible to introduce the ceramic rod into a prefabricated tube whose internal diameter is slightly larger than the external diameter of the ceramic rod, and then to warm the plastic so that the tube can be reduced to the final diameter and thus tightly surrounds the ceramic rod.

In a further variant, the plastic casing is produced by flame spraying or single or multiple shrinking-on.

5 The pores of the outer surface of the monolithic sorbent can also be sealed by coating with a resin or a polysiloxane or another substance which solidifies to form an impermeable, pore-free layer. It is also possible to coat the outer surface of a monolithic
10 sorbent consisting of ceramic material with a glass having the lowest possible melting point; in this case, the glass should preferably have a similar coefficient of thermal expansion to the monolithic sorbent.

15 Working methods and parameters are known to the person skilled in the art of plastics processing or can be optimized by conventional methods.

In principle, it is also possible to carry out the
20 last-mentioned variants of the encasing after a prior first encasing with, for example, a shrink tube or similar non-pressure-resistant material.

The monolithic sorbent encased in a pressure-resistant
25 manner can be provided with end pieces for connecting eluent feed and outlet lines (chromatography column with monolithic sorbent). End pieces can be screwed on, bonded on or shrunk on.

30 It is also possible to equip the monolithic sorbent encased in a pressure-resistant manner as a chromatographic cartridge for accommodation in a cartridge holding device. To this end, the casing can be provided, for example, with an annular groove in
35 which corresponding projections of the cartridge holding device engage. Sealing elements at the ends can, for example, be bonded or pressed in.

Suitable designs of chromatographic columns or cartridges and their end pieces are known to the person skilled in the art and are described in the relevant literature; thus, for example, cartridges and cartridge holders are disclosed in EP 0 205 002, EP 0 268 185 and EP 0 068 343.

The encasing of a monolithic sorbent in PEEK is described below by way of example: a monolithic moulding (100 x 7.2 mm) is introduced into a PEEK tube (internal diameter 7.4 mm, wall thickness 1.5 mm). The plastic tube and moulding are warmed to about 300 - 400°C, and the plastic tube is pressed tightly onto the moulding in a pressure device. After cooling, the encased moulding is cut to a length of 83 mm.

A monolithic sorbent encased in this way can be introduced directly into a cartridge holding device as shown by way of example in Figure 1. The upper half of the device is shown. The monolithic sorbent (1) is covered by the plastic casing (7) in a liquid-impermeable manner. A distributor frit (11) is located on the front face of the monolithic sorbent, and a ring seal (12) is supported on the face of the plastic casing. The distributor frit (11) and seal (12) are located in a recess in the end piece (9), which has a connector (10) for eluent feed and outlet. The encased monolithic sorbent is located in a tube (8), for example made of aluminium or stainless steel, which is sealed by a screw cap (13). The screw cap (13) presses the end piece (9) against the plastic casing (7) and the monolithic sorbent (1).

The encasing of the monolithic sorbent can also be carried out in such a manner that it is, for example, in principle possible to re-use the casing; a design of this type is shown in Figure 2 (shown without accommodation device for eluent feed and outlet):

A self-sealing holding device into which the monolithic sorbent (1) can be inserted consists, for example, of the following constituents:

- 5 (2) a tube of ductile or elastic inert material, for example Teflon or silicone rubber, which is conical at both ends;
- (3) two terminal pieces in the shape of truncated cones with a passage for eluent feed and discharge, made of ductile or elastic inert
- 10 material, for example Teflon or silicone rubber;
- (4) a stainless-steel tube;
- (5) two threaded connections between the stainless-steel tube (4) and the end caps
- 15 (6);
- with the same function, for example, an external holding device or screw rods between the end caps/end plates;
- (6) two stainless steel end caps.
- 20 Instead of using stainless steel, other customary materials for chromatographic columns can be used.

25 This holding device allows the monolithic sorbent (1) to be inserted into the tube (2). For disposal, the monolithic sorbent can be pushed out of the tube after use. The tube (2) and the terminal pieces (3) can be re-used, as can the stainless-steel parts (4) and (6).

30 The internal length of the tube (2) is longer than the ceramic rod (1). When the end caps (6) are screwed onto the tube (4), the terminal pieces (3) compress the tube (2). Owing to the ductility of the materials, the monolithic sorbent is held in the device in a sealing manner.

35

A similar device is shown in Figure 3 (one half): the monolithic sorbent (1) is located in a tube (15) of a flexible, solvent-resistant material, which is itself located in a tube (14). A distributor frit (11) and a

connecting piece (17) with connecting tube (18) is located on each of the faces of the monolithic sorbent. The connecting piece (17) is held by the head piece (16). Pressure rams (19) press the tube (15) firmly
5 against the monolithic sorbent.

Even without further explanations, it is assumed that a person skilled in the art can use the above description in the broadest extent. The preferred embodiments and
10 examples are therefore to be regarded merely as a descriptive disclosure which is in no way limiting in any way.

The entire disclosure content of all applications,
15 patents and publications mentioned above and below and the corresponding application DE 197 26 164.7, submitted on 20.06.97, are incorporated into this application by way of reference.

Claims

1. Encased monolithic sorbent based on porous mouldings which have interconnected macropores and mesopores in the walls of the macropores, where the diameter of the macropores has a median value of greater than 0.1 μm and where the diameter of the mesopores has a median value of 2 and 100 nm, characterized in that the outer surface of said monolithic sorbent is surrounded in a liquid-impermeable manner by a pressure-resistant plastic casing.
2. Use of a monolithic sorbent according to Claim 1 in a chromatographic column or a chromatographic cartridge.
3. Use of a monolithic sorbent according to Claim 1 in the chromatographic separation of at least two substances.

Holding device for monolithic sorbents

Abstract

The invention relates to encased monolithic sorbents based on porous mouldings, where the outer surface of said monolithic sorbent is surrounded in a liquid-impermeable manner by a pressure-resistant casing, for example of plastic. The casing according to the invention is in particular in the case of porous mouldings which have interconnected macropores and mesopores in the walls of the macropores, where the diameter of the macropores has a median value of greater than 0.1 μm and where the diameter of the mesopores has a median value of 2 and 100 nm. The invention furthermore relates to the use of a monolithic sorbent according to the invention in a chromatographic column or a chromatographic cartridge, and to the use of a monolithic sorbent according to the invention in the chromatographic separation of at least two substances.

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY
(Includes Reference to: PCT International Applications)ATTORNEY'S DOCKET NUMBER
MERCK-2047

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought of the invention entitled:

HOLDING DEVICE FOR MONOLITHIC SORBENTS

the specification of which (check only one item below):

☐ is attached hereto☐ was filed as United States application

Serial No. _____

on _____

and was amended

on _____ (if applicable).

☒ was filed as PCT international applicationNumber PCT/EP98/03525on 10 JUNE 1998

and was amended under PCT Article 19

on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:

COUNTRY (if PCT, indicate "PCT")	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED UNDER 35 USC 119
GERMANY	DE 197 26 164.7	02 JUNE 1997	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
			<input type="checkbox"/> YES <input type="checkbox"/> NO
			<input type="checkbox"/> YES <input type="checkbox"/> NO
			<input type="checkbox"/> YES <input type="checkbox"/> NO
			<input type="checkbox"/> YES <input type="checkbox"/> NO

Combined Declaration For Patent Application and Power of Attorney (Continued)ATTORNEY'S DOCKET NUMBER
MERCK-2047

(Includes Reference to PCT International Applications)

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in said/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application:

U.S. APPLICATION NUMBER	U.S. FILING DATE	PATENTED	PENDING	ABANDONED
PCT APPLICATION NO.	PCT FILING DATE	U.S. SERIAL NUMBERS ASSIGNED (if any)		

POWER OF ATTORNEY. As a named inventor, I hereby appoint: William Millen (19,544); John L. White (17,746); Anthony J. Zelano (27,969); Allen E. J. Branigan (20,565); John R. Moses (24,983); Harry B. Shubin (32,004); Brian P. Heaney (32,542); Richard J. Traverso (30,595); John A. Sopp (33,103); Richard M. Lepovitz (37,067); John H. Thomas (33,460); James T. Moore (35,619); Catherine M. Joyce (40,668); Nancy J. Axelrod (44,014); James E. Ruland (37,432) and Jennifer J. Branigan (40,921) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

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703/243-6333

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Anthony J. Zelano

2	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
0	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
1	POST OFFICE ADDRESS	STREET	CITY	STATE & ZIP CODE/COUNTRY
		c/o Merck KGaA, Frankfurter Str. 250	Darmstadt	64293 GERMANY
2	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
0	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
2	POST OFFICE ADDRESS	STREET	CITY	STATE & ZIP CODE/COUNTRY
		c/o Merck KGaA, Frankfurter Str. 250	Darmstadt	64293 GERMANY
2	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
0	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
3	POST OFFICE ADDRESS	STREET	CITY	STATE & ZIP CODE/COUNTRY
		c/o Merck KGaA, Frankfurter Str. 250	Darmstadt	64293 GERMANY
2	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
0	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
4	POST OFFICE ADDRESS	STREET	CITY	STATE & ZIP CODE/COUNTRY
		c/o Merck KGaA, Frankfurter Str. 250	Darmstadt	64293 GERMANY
2	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
0	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
5	POST OFFICE ADDRESS	STREET	CITY	STATE & ZIP CODE/COUNTRY
		c/o Merck KGaA, Frankfurter Str. 250	Darmstadt	64293 GERMANY

Combined Declaration for Patent Application and Power of Attorney (Continued)

(Includes Reference to PCT and National Applications)

 ATTORNEY'S DOCUMENT NUMBER
 MERCK-2047

206	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	STREET	CITY	STATE & ZIP CODE/COUNTRY
207	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	STREET	CITY	STATE & ZIP CODE/COUNTRY
208	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	STREET	CITY	STATE & ZIP CODE/COUNTRY
209	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	STREET	CITY	STATE & ZIP CODE/COUNTRY
210	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	STREET	CITY	STATE & ZIP CODE/COUNTRY
211	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	STREET	CITY	STATE & ZIP CODE/COUNTRY

I hereby declare that all statements made herein or my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

SIGNATURE OF INVENTOR 201	DATE	SIGNATURE OF INVENTOR 207	DATE
SIGNATURE OF INVENTOR 202	DATE	SIGNATURE OF INVENTOR 208	DATE
SIGNATURE OF INVENTOR 203	DATE	SIGNATURE OF INVENTOR 209	DATE
SIGNATURE OF INVENTOR 204	DATE	SIGNATURE OF INVENTOR 210	DATE
SIGNATURE OF INVENTOR 205	DATE	SIGNATURE OF INVENTOR 211	DATE
SIGNATURE OF INVENTOR 206	DATE	SIGNATURE OF INVENTOR 212	DATE